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Exhaled Nitric Oxide: A Marker of Pulmonary Hemodynamics in Heart Failure

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OBJECTIVES We sought to test the hypothesis that patients with decompensated heart failure (HF) lose a compensatory process whereby nitric oxide (NO) maintains pulmonary vascular tone.

BACKGROUND Exhaled nitric oxide (eNO) partially reflects vascular endothelial NO release. Levels of eNO are elevated in patients with compensated HF and correlate inversely with pulmonary artery pressures (PAP), reflecting pulmonary vasodilatory activity.

METHODS We measured the mean mixed expired NO content of a vital-capacity breath using chemiluminescence in patients with compensated HF (n = 30), decompensated HF (n = 7) and in normal control subjects (n = 90). Pulmonary artery pressures were also measured in patients with HF. The eNO and PAP were determined sequentially during therapy with intravenous vasodilators in patients with decompensated HF (n = 7) and in an additional group of patients with HF (n = 13) before and during administration of milrinone.

RESULTS The eNO was higher in patients with HF than in control subjects (9.9 ± 1.1 ppb vs. 6.2 ± 0.4 ppb, $p = 0.002$) and inversely correlated with PAP ($r = -0.81$, $p < 0.00001$). In marked contrast, patients with decompensated HF exhibited even higher levels of eNO (20.4 ± 6.2 ppb) and PAP, but there was a loss of the inverse relationship between these two variables. During therapy (7.3 ± 6 days) with sodium nitroprusside and diuresis, hemodynamics improved, eNO concentrations fell (11.2 ± 1.2 ppb vs. before treatment, $p < 0.05$), and the relationship between eNO and PAP was restored. After milrinone, eNO rose proportionally with decreased PAP ($p < 0.05$).

CONCLUSIONS Elevated eNO may reflect a compensatory circulatory mechanism in HF that is lost in patients with clinically decompensated HF. The eNO may be an easily obtainable and quantifiable measure of the response to therapy in advanced HF. (J Am Coll Cardiol 2002; 40:1114–9) © 2002 by the American College of Cardiology Foundation

The circulation in congestive heart failure (HF) is characterized by increases in both systemic and pulmonary vascular tone (1), changes mediated by humoral and neurogenic signals that include the renin-angiotensin-aldosterone system, the sympathetic nervous system, and endothelin (2). A primary counter-regulatory mechanism mediating vascular relaxation is endothelial release of nitric oxide (NO) (3–5). Both agonist-induced and baseline NO production have been studied in HF. Whereas agonist-stimulated vascular NO release is impaired, as indicated by diminished acetylcholine-mediated vasodilatory responses, baseline NO release may be elevated in HF (6–9). In this regard, the vasoconstrictive response to N^G-monomethyl-L-arginine (L-NMMA), an inhibitor of NO synthesis, is exaggerated in patients with HF (10), and plasma nitrate, a stable end product of NO production, is increased in patients with HF (11).

Nitric oxide measured in exhaled air (eNO) reflects production by both the airway and vascular endothelial cells (12). Patients with HF demonstrate inverse correlations between eNO and pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR), consistent with biological activity of NO to produce vasodilation (13). Other findings support this relationship between eNO and NO release by the vasculature. For example, levels of eNO rise with administration of both the NO synthase precursor L-arginine and nitrates (14–16), and exercise enhances eNO, likely due to vasodilatory endothelial release (17,18).

As the neurohormonal factors that contribute to the transition from "compensated" to "decompensated" HF are not fully explained, we sought to test whether patients with advanced HF would demonstrate a loss of the relationship between pulmonary artery pressure (PAP), which rises with advancing HF, and eNO, suggesting an impairment of compensatory NO production in HF. Moreover, we tested whether treatment of HF would restore the relationship between PAP and eNO, suggesting a restoration of a compensatory process and the possibility that eNO could be used as a clinical marker of HF severity and responsiveness to treatment.

METHODS

Subjects. A historic control group from a previous study by Massaro et al. (19) consisted of 58 women and 32 men

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Abbreviations and Acronyms

cGMP = cyclic guanosine 3′,5′-monophosphate
eNO = exhaled nitric oxide
FEV_1 = forced expiratory volume in 1 s
FVC = forced vital capacity
HF = heart failure
L-NMMA = N^G-monomethyl-L-arginine
NO = nitric oxide
NYHA = New York Heart Association
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
SNP = sodium nitroprusside
SVR = systemic vascular resistance

(average age 30.9 years [range 19 to 65 years]) with no history of heart problems (19). The compensated HF group consisted of inpatients and outpatients (n = 30) being managed for HF. These patients underwent diagnostic right-heart catheterization on the day of eNO measurement to obtain right- and left-sided filling pressures, PAP, and cardiac output. A confirmatory case-control study was conducted in patients with HF (n = 5; mean age 37.2 years) matched with control subjects (n = 5; mean age 39.4 years) who were family members exposed to similar environmental conditions. The patients with decompensated HF (n = 7) comprised patients admitted to the Cardiac Critical Care Unit to undergo therapy with intravenous agents during invasive cardiac monitoring with a pulmonary artery catheter. These patients were prospectively selected based on signs and symptoms of profound volume overload or low cardiac output (20). All subjects gave written, informed consent for participation in the protocol, as approved by the Committee for the Protection of Human Subjects From Research Risks at Brigham and Women's Hospital, Boston.

Determination of eNO levels. Levels of NO were measured in mixed expired air from all subjects, as previously described by Massaro et al. (19). The method of NO measurements in both historic control groups and the group with compensated HF were identical. Five patients with HF and their matched control subjects underwent NO measurements after performing deep breathing for ~1 min through a one-way valve from a Douglas bag filled with NO-free air (<0.5 ppb).

Tailored HF therapy protocol. Patients with decompensated HF in the critical care setting were placed on tailored therapy for HF (21). Baseline hemodynamic variables were measured as described by Stevenson et al. (20). Intravenous sodium nitroprusside (SNP) and diuretics were administered in dosages tailored to achieve an optimal SVR ≤1,200 dynes-s per cm^5 and systolic blood pressure ≥80 mm Hg within 24 to 48 h. Once SVR was optimized, patients were weaned off SNP and started on captopril. Serial measurements of eNO were determined using the protocol described by Massaro et al. (19).

Milrinone therapy protocol. Thirteen additional patients with HF were treated with milrinone. Each underwent right-heart catheterization and received milrinone by a bolus injection of 50 μg/kg over 1 min (22). Hemodynamic variables and eNO were measured at baseline and after 20 min by the methods described earlier.

Table 1. Baseline Characteristics of Study Group

	Patients With Compensated HF (n = 30)	Patients With Decompensated HF (n = 7)
Age (yrs)	53 ± 1	51 ± 4
Male gender (%)	64	86
NYHA functional class (%)		
I–II	20	0
III–IV	80	100
CHF etiology (%)		
Cardiomyopathy	55	29
CAD	20	57
Other	25	14
RAP (mm Hg)	11.1 ± 1.2	16.6 ± 2.8*
PAP, systolic (mm Hg)	42.2 ± 2.8	61.4 ± 3.3*
PAM (mm Hg)	30.0 ± 2.2	43.5 ± 2.5*
PCWP (mm Hg)	20.6 ± 2.0	31.0 ± 3.0*
PVR (dynes-s per cm^5)	252 ± 49	356 ± 47
CO (l/min)	4.2 ± 0.4	3.0 ± 0.3*
FEV_1/FVC ratio	0.82 ± 0.02	0.83 ± 0.03

*$p < 0.05$ vs. compensated HF group. Data are presented as the mean value ± SEM or percentage of patients.

CAD = coronary artery disease; CHF = congestive heart failure; CO = cardiac output; FEV_1/FVC = forced expiratory volume in 1 s to forced vital capacity ratio; HF = heart failure; NYHA = New York Heart Association; PAM = mean pulmonary aterial pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

Statistical analysis. Data are expressed as the mean value ± SEM in the patient study group and as the mean value ± SD in the matched control group. The unpaired two-tailed Student *t* test was used to analyze the differences in eNO levels between the historic control group and HF group. Comparisons between patients with HF and their matched control subjects were calculated using the paired two-tailed Student *t* test. Analysis of patients with HF at baseline, during SNP treatment, and after therapy were performed with analysis of variance. Post-hoc analysis was performed using the Student-Newman-Keuls test. The relationship between eNO and PAP was tested using linear regression. Multiple linear regression was used to test for the independent impact of age, gender, forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and concomitant use of nitrates on the relationship between eNO and PAP. A level of $p < 0.05$ was accepted as statistically significant.

RESULTS

Study group. The baseline characteristics of the study patients are shown in Table 1. The eNO was significantly elevated in the compensated HF group compared with the control group (9.9 ± 1.1 ppb vs. 6.2 ± 0.4 ppb, $p = 0.0002$) (Fig. 1), and PAP inversely correlated with eNO ($r = -0.81$, $p < 0.00001$) (Fig. 2). Exhaled NO did not correlate with New York Heart Association (NYHA) functional

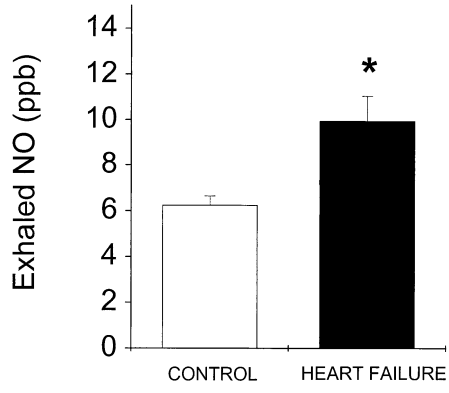

Figure 1. Comparison of baseline exhaled nitric oxide (NO) in patients with heart failure versus normal control subjects. The baseline exhaled NO was significantly increased in the heart failure group. *p = 0.0002.

class. In a multiple linear regression analysis, PAP remained independently associated with eNO after adjustment for age, gender, FEV_1, FEV_1/FVC ratio, and concomitant use of nitrates.

Matched control study. The aforementioned results were confirmed in a small case-control study in which all patients with HF exhibited higher levels of eNO, as compared with their matched control subjects (8.4 ± 3.5 ppb vs. 6.5 ± 2.4 ppb, $p < 0.04$).

eNO in patients with decompensated HF. Despite higher systolic PAP, patients with decompensated HF (Table 1) did not have low eNO levels. In contrast, the highest eNO levels were observed among these patients. In addition, there was no correlation between eNO and PAP in these patients (Fig. 2). Moreover, combining the systolic PAP and eNO data from the patients with decompensated and compensated HF eliminated the linear relationship between these variables ($r = 0.01$, $p = 0.95$).

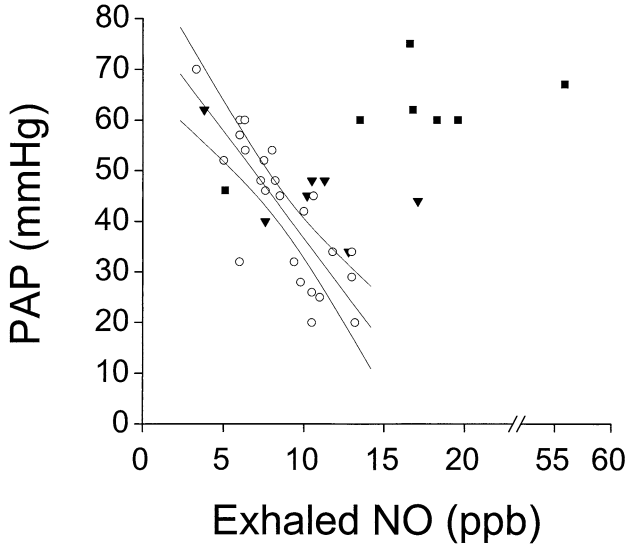

Figure 2. Scatterplot demonstrating the correlation ($r = -0.81$, $p < 0.00001$) between levels of exhaled nitric oxide (NO) and systolic pulmonary artery pressure (PAP) in patients with compensated heart failure **(open circles)**. Linear regression lines with 95% confidence intervals are depicted for patients with compensated heart failure. Patients with decompensated heart failure at baseline **(solid squares)** deviated from this curve, did not exhibit an inverse correlation between eNO and PAP, and eliminated the linear relationship between PAP and eNO. The relationship between these two variables was restored toward normal after tailored therapy **(solid inverted triangles)**. With inclusion of the post-treatment data, the linear regression between NO and PAP persisted ($r = -0.66$, $p = 0.00005$).

To assess whether treatment that improved hemodynamics in HF restored the relationship between eNO and PAP, we serially monitored eNO concentrations during hemodynamically guided vasodilator therapy in these patients. The eNO progressively decreased during SNP therapy (11.2 ± 1.2 ppb vs. 20.4 ± 6.2 ppb at baseline, $p < 0.05$) (Fig. 3). This was accompanied by a reduction of PVR, improved cardiac output, and decreased pulmonary capillary wedge pressure (Table 2). Early administration of SNP did not increase eNO values (Table 2).

Although baseline levels of eNO did not correlate with PAS in this group, the relationship was restored after therapy (Fig. 2). With inclusion of the post-treatment data in the linear regression between eNO and PAP, this relationship persisted ($r = -0.66$, $p < 0.0001$). The baseline FEV_1/FVC ratios in these patients with decompensated HF did not change significantly after therapy (0.83 ± 0.03 vs. 0.77 ± 0.07, $p = 0.43$).

Response of eNO and PAP to milrinone. In 13 additional patients given milrinone to reduce PAP, there was a significant inverse correlation between the change in eNO and the change in PAP ($r = -0.61$, $p = 0.027$), such that the greater the PAP reduction, the greater the increase in eNO (Fig. 4). In patients in whom PAP did not change or actually increased, eNO declined. In contrast to the relationship with PAP, eNO did not correlate with changes in cardiac output in response to milrinone.

DISCUSSION

This study demonstrates that patients with advanced decompensated HF have profoundly elevated baseline eNO levels, in contrast to patients with all other degrees of HF (NYHA functional classes I to IV). In contrast to patients with compensated HF who exhibit a correlation between PAP and eNO, patients with decompensated HF do not. However, with treatment that restores hemodynamics, eNO levels fall, and the relationship between eNO and PAP is restored. Thus, measurement of eNO may be useful as an indicator of progressive HF and has the potential to predict the response to treatment.

Several groups have previously investigated levels of eNO in HF. Funakoshi et al. (18) showed eNO to be elevated in HF. Three other studies, however, demonstrated that eNO was either decreased or unchanged in patients with HF (13,23,24). Our findings demonstrate that patients with HF have wide ranges of eNO, possibly explaining the discrepancy in previous studies. Our results are consistent with other assessments of NO production or bioactivity in HF.

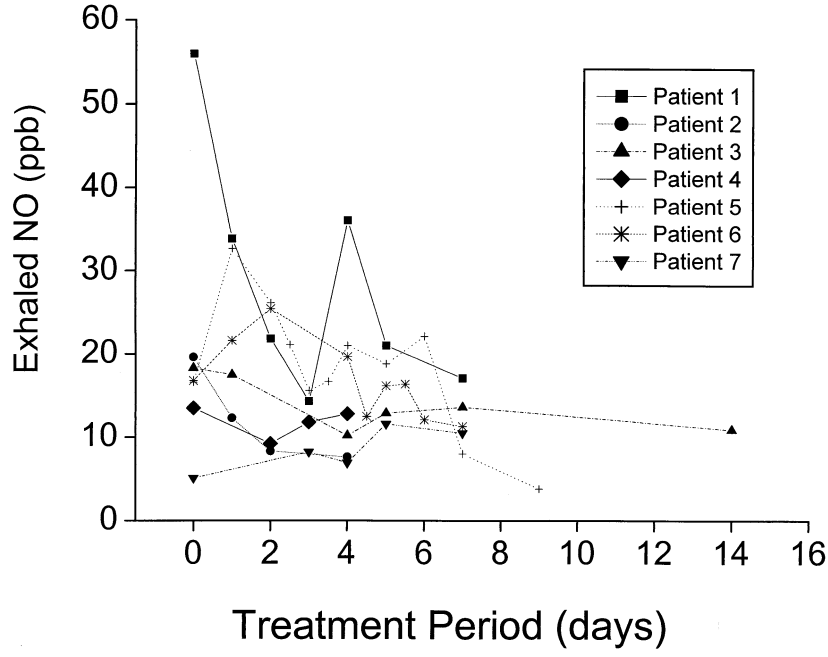

Figure 3. Individual nitric oxide (NO) curves among patients with heart failure (n = 7) in response to tailored therapy showing a progressive decline in exhaled NO concentrations during heart failure treatment.

Winlaw et al. (11) found plasma nitrates to be increased in patients with HF compared with normal subjects. The increased vasoconstrictive response to L-NMMA in patients with HF also supports our conclusion that baseline production of NO is enhanced in HF (10). Finally, Cooper et al. (5) demonstrated that NO activity was diminished in patients with HF and an elevated PVR index, but was preserved in those with a normal PVR index, a finding that correlates with our hypothesis that NO activity plays a compensatory role in maintaining pulmonary vascular tone.

Loss of the inverse relationship between eNO and PAP among patients with decompensated HF. Although baseline eNO was higher in the HF group compared with the control group, within the HF group, eNO levels inversely correlated with PAP. This finding supports the compensatory role of endothelial NO release in reducing PAP in compensated HF, suggesting that eNO reflects bioactive endothelial NO release capable of producing vascular relaxation. In contrast, patients with decompensated HF deviated from this linear relationship and demonstrated a marked elevation of both eNO and systolic PAP. This finding likely reflects a loss of biological efficacy of NO in these subjects. Treatment of these patients with decompensated HF restored the inverse relationship between eNO and PAP, consistent with a return to the compensated state.

We also observed an inverse correlation between the

Table 2. Response of Exhaled Nitric Oxide and Hemodynamic Variables to Heart Failure Therapy

	Before Therapy	SNP for 2 h	After Therapy
NO (ppb)	20.4 ± 6.2	22.8 ± 4.6	11.2 ± 1.2*
PVR (dynes-s per cm^5)	356 ± 47	287 ± 63	147 ± 32*
CO (l/min)	3 ± 0.3	4.64 ± 0.9	4.8 ± 0.3†
PCWP (mm Hg)	31 ± 3	27 ± 2	21 ± 7†

*$p < 0.05$ vs. baseline and SNP and †$p < 0.05$ vs. baseline (analysis of variance with the Student-Newman-Keuls post-hoc test). Data are expressed as the mean value ± SEM.

NO = nitric oxide; SNP = sodium nitroprusside; other abbreviations as in Table 1.

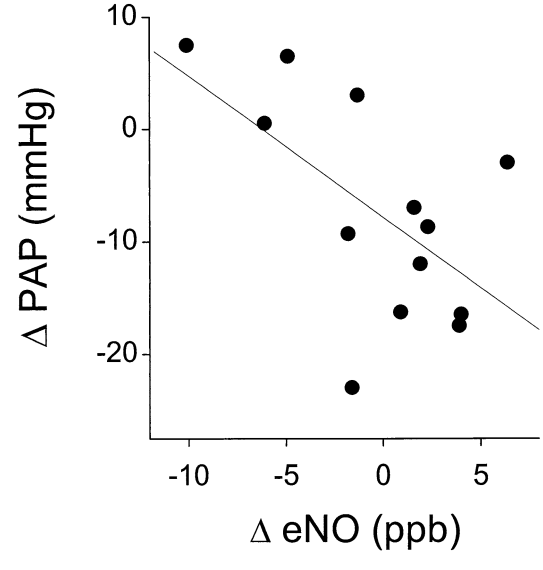

Figure 4. Scatterplot demonstrating the inverse correlation between the change in pulmonary artery pressure (PAP) and exhaled nitric oxide (eNO) in response to acute administration of milrinone ($r = -0.61$, $p = 0.027$). A decrease in PAP caused by milrinone was associated with a rise in eNO, consistent with the inverse relationship depicted in Figure 1. In patients in whom PAP remained unchanged or rose slightly with milrinone, eNO actually fell, consistent with the notion that these patients have a defect in nitric oxide pathway activity.

JACC Vol. 40, No. 6, 2002
September 18, 2002:1114–9

change in PAP and eNO after early administration of milrinone, a pulmonary vasodilator. This finding reinforces our conclusion that eNO levels may reflect vascular reactivity. This finding is relevant because milrinone is not a precursor in the NO pathway. Furthermore, it is also unlikely that a change in cardiac output affected the change in eNO, because there was no correlation between these variables.

Our findings demonstrate that NO production is intact and possibly elevated in patients with decompensated HF. The concurrent loss of the inverse correlation with PAP suggests compromised NO activity. Cyclic guanosine 3′,5′-monophosphate (cGMP), the second messenger mediating vascular smooth muscle relaxation, is also elevated in the plasma of patients with HF (25–28). These findings suggest that a defect in the NO pathway may occur downstream of cGMP signaling. Although confounding factors such as airway inflammation and bronchospasm secondary to pulmonary edema may also cause eNO to rise and subsequently fall with treatment, this explanation is less likely, because baseline FEV_1/FVC ratios in patients with decompensated HF did not exhibit obstructive patterns and did not change significantly after therapy (29).

eNO as a marker of endothelial function. This study supports the relationship between eNO and endothelial NO production. Other evidence for this association comes from observations that eNO rises with administration of NO precursors and with exercise. However, a recent study involving healthy subjects has shown that although L-NMMA infusion elicits appropriate hemodynamic changes, it does not concomitantly affect eNO (30). Furthermore, Dirnberger et al. (31) observed that intravenous infusion of nitrates does not increase eNO among healthy subjects. A recent study has also suggested that exercise-induced increases in eNO more likely result from increased expiratory air flow rates than from endogenous NO production (32). However, these studies were performed in healthy subjects, and their results may not take into account the intrinsic differences in NO production in HF. The inverse correlation between levels of eNO and PAP supports the idea that eNO reflects endothelial release. This finding is in agreement with the data of Sumino et al. (13), who found a similar relationship between the rate of NO release and peripheral vascular resistance. The decrease in eNO associated with the clinical response to HF therapy, as measured by established hemodynamic parameters provides additional evidence that NO produced in the lower airways is a marker of vascular endothelial function. However, the response of NO to hemodynamic improvement may also reflect a decrease in bronchial hyper-responsiveness caused by pulmonary vascular congestion. Our data further imply that the loss of the relationship between eNO and PAP is a reflection of a loss of vascular reactivity due to either diminished activity of NO or augmented activity of other neurohumoral factors.

Study limitations. The use of historic data in this study raises the concern of confounding factors. A multiple linear regression analysis, however, did not show an influence of age, gender, and use of nitrates on eNO levels. We also confirmed our findings in a subsequent matched control study. Furthermore, our study did not address whether other neurohumoral factors, such as angiotensin II, endothelin-1, norepinephrine, and brain natriuretic peptide, contributed to elevated PAP in patients with decompensated HF and thus the loss of the inverse relationship between eNO and PAP. The number of patients with decompensated HF may also have been too small to detect either a negative or positive correlation between eNO and PAP in this population.

Clinical implications. Despite advances in HF treatment, reliable noninvasive markers of therapy are only recently becoming available. Most end points for treatment are based on the clinical symptoms of the patient, and this approach may fall short of adequate therapy that is needed to optimize hemodynamics. Traditionally, invasive monitoring (with Swan-Ganz catheters) has been used to guide therapy. However, invasive monitoring is not without risk or expense, and other markers of successful treatment are needed. Biological markers such as brain natriuretic peptide will play an important role in monitoring and tailoring HF therapy in the future (33).

Although the correlation between eNO levels and clinical improvement has been demonstrated in noncardiac conditions such as asthma, our study is the first to report the use of measured eNO as an indicator of decompensation in HF and as a marker of the response to treatment (19,29). This biological marker is particularly useful in selecting patients for inpatient HF therapy. A patient in the compensated state would typically be represented on the linear curve that reflects the inverse correlation between NO and PAP. Serial NO measurements may be able to detect when a patient deviates from this curve and may predict progression to decompensated HF. Furthermore, a decrease in eNO after therapy correlates with hemodynamic improvement, providing a noninvasive marker of therapeutic efficacy. Future studies to refine the NO-PAS relationship and to define the values associated with decompensation yield the potential for developing a simple system to detect advanced HF and therapeutic responsiveness.

Conclusions. The eNO is elevated in patients with compensated HF, and there is an inverse correlation between eNO and PAP. This relationship is lost in patients with decompensated HF and is subsequently restored after hemodynamic improvement with tailored therapy. Furthermore, the response of eNO to a pulmonary artery vasodilator inversely correlates with the change in PAP. Our study provides further evidence that eNO is a marker of endothelial function.

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